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Induction of hepatic drug metabolizing enzymes by DL-methionine in rats

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Abstract. A single intraperitoneal injection of DL-methionine (500 mg/kg body wt.) to adult male Wistar rats was shown to significantly induce all the components of the hepatic microsomal mixed function oxidase system such as NADPH cytochrome *C* reductase activity, cytochromes P-450 and b_5, as well as activities of drug metabolizing enzymes such as aminopyrine demethylase and uridine 5′-diphosphate-glucuronosyltransferase. Combined administration of nicotinamide (250 mg/kg body wt.) and DL-methionine (500 mg/kg body wt.) was shown to bring about an additional increase (25-30%) in the activities of these enzymes as compared to their induction on independent administration of the two endobiotics. In rats bearing Yoshida sarcoma (ascites) tumour as well as in normal rats injected with serum from tumour bearing animals, the decreased activities of hepatic mixed function oxidases could be restored to their normal levels by administration of DL-methionine (500 mg/kg body wt.) to these rats. Whereas actinomycin D (1 mg/kg body wt.) had no effect on the increased incorporation of [^{14}C] labelled leucine into microsomal proteins following administration of nicotinamide, the enhanced incorporation of the label following DL-methionine administration was completely inhibited by the same dose of actinomycin D. Administration of cycloheximide (0·5 mg/kg body wt.) to rats could completely inhibit the increased incorporation of [^{14}C] leucine into hepatic microsomal proteins following independent administration of nicotinamide and DL-methionine. Similar inhibitory pattern with actinomycin D and cycloheximide was also demonstrated in case of induction of NADPH cytochrome *C* reductase activity by both these endobiotics.

Keywords. Mixed function oxidases; drug metabolizing enzymes; induction by methionine; tumour-bearing rats; host livers; methionine and nicotinamide; combined effect.

Introduction

Induction of drug metabolizing enzymes by exogenous compounds like drugs, carcinogens and environmental chemicals is well documented using experimental animal systems (Parke, 1975; Depierre and Ernster, 1978; Conney, 1986, Okey *et al.*, 1986). Several naturally occurring nutrients have also been shown to enhance the activities of drug metabolizing enzymes (Mitoma *et al.*, 1969; Parke and Rahman, 1969; Feuer, 1970; Wattenberg, 1972; Parke *et al.*, 1974; Hsiao *et al.*, 1975; Hvang *et al.*, 1981). Earlier studies from this laboratory demonstrated that a single intraperitoneal (i.p.) administration of nicotinamide, a vitamin and an endobiotic could effectively bring about induction of all the components of hepatic mixed function oxidases (MFO) system such as cytochromes P-450, b_5 and NADPH cytochrome *C* reductase activity (Kamat *et al.*, 1980). The activities of hepatic microsomal arylhydrocarbon hydroxylase, aminopyrine demethylase as well as drug conjugating enzymes like uridine 5′-diphosphate (UDP)-glucuronosyltransferase

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Abbreviations used: i.p., Intraperitonial; MFO, mixed function oxidases; UDP, uridine 5′-diphosphate.